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EXAMINER
UNGAR, SUSAN NMN

ART UNIT	PAPER NUMBER
1642	

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17

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/509,779	Applicant(s) Sun
	Examiner Ungar	Art Unit 1642

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *three* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Jun 11, 2002* .

2a) ☐ This action is **FINAL.** 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *2-6, 8-17, 25-27, 32, and 38-40* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *2-6, 8-17, 25-27, 32, and 38-40* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

1. The Amendment filed June 11, 2002 (Paper No. 15) in response to the Office Action of January 11, 2002 (Paper No. 13) is acknowledged and has been entered. Previously pending claims 1, 7, 18-24, 27-31, 33-37 have been canceled, claims 2, 4, 5, 8, 10-11, 17, 25 have been amended and new claims 38-40 have been added. Claims 2-6, 8-17, 25-26, 32 and 38-40 are currently being examined.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

3. It is noted that neither the instant application nor the parent to which priority is claimed were submitted with drawings or figures. However, it is noted that figures are referred to in the specification. Applicant is required to delete all mention of figures since they were never submitted and if now submitted would be new matter.

4. The following rejections are maintained:

Claim Rejections - 35 USC § 112

5. Claims 6 and 12-14 remain rejected under 35 USC 112, first paragraph for the reasons previously set forth in paper No. 13, Section 10, pages 4-6.

Applicant argues that a copy of the relevant deposit receipt displaying a deposit date before the time of filing for these accession numbers is attached herewith. The argument has been considered but has not been found persuasive because the submitted receipt is insufficient to meet all the criteria set forth in MPEP 608/01(p)(C) (please see Paper No. 10, pages 5-6) and no declaration, that meets those criteria has been submitted. If a deposit has been made under the provisions of the Budapest Treaty, filing of an affidavit or declaration by applicant

or assignees or a statement by an attorney of record who has authority and control over the conditions of deposit over his or her signature and registration number stating that the deposit has been accepted by an International Depository Authority under the provisions of the Budapest Treaty, that all restrictions upon public access to the deposits will be irrevocably removed upon the grant of a patent on this application and that the deposit will be replaced if viable samples cannot be dispensed by the depository is required. This requirement is necessary when deposits are made under the provisions of the Budapest Treaty as the Treaty leaves this specific matter to the discretion of each State.

In addition to the conditions under the Budapest Treaty, applicant is required to satisfy that all restrictions imposed by the depositor on the availability to the public of the deposited material will be irrevocably removed upon the granting of a patent in U.S. patent applications. Applicant's arguments have not been found persuasive and the rejection is maintained. Applicant's provision of these assurances would obviate this objection/rejection.

6. Claims 2, 4-5, 8, 10-11, 25-26 and 32 remain rejected under 35 USC 112, first paragraph and newly added claims 39-40 are rejected under 35 USC 112, first paragraph, for the reasons previously set forth in paper No. 13, Section 11, pages 6-7.

Applicant argues that the claims have been amended as to hybridization conditions and that claims 25, 26 and 32 have been amended with regard to primers being derived from a sequence. The arguments have been considered but have not been found persuasive because the claims as written still read on nucleic acid

sequences which minimally contain only portions of SEQ ID NO:1 or 3 and the claims are still drawn to a large genus of molecules. As drawn to claims 39 and 40 which limit the claimed nucleic acid molecule to one that encodes a polypeptide that protects a cell from apoptosis when produced in said cell (claim 39) and a molecule which encodes a polypeptide that protects against lipid peroxidation, a review of the specification has revealed that motif searching of the deduced protein sequences using the GCG program, did not reveal any known functional domains, although the putative proteins each contain two imperfect heme binding sites and one imperfect zinc ring finger domain (p. 15, lines 27-3). Applicant has clearly demonstrated no structures have been identified that are specifically drawn to either an apoptosis protective function or a lipid peroxidation protective function. The instant specification fails to provide sufficient descriptive information, such as definitive structural features of the claimed genus of polynucleotides. There is no description of the conserved regions which are critical to the structure and function of the genus claimed. The specification proposes to discover other members of the genus by using conventional techniques and screening. There is no description, however, of the sites at which variability may be tolerated and there is no information regarding the relation of structure to function. Structural features that could distinguish the compounds in the genus from others excluded are missing from the disclosure. Furthermore, the prior art does not provide compensatory structural or correlative teachings sufficient to enable one of skill to isolate and identify the polynucleotides encompassed and no identifying characteristic or property of the instant polynucleotides is provided such that one of skill would be able to predictably

identify the encompassed molecules as being identical to those instantly claimed. and therefore one would conclude that Applicant was not in possession of the claimed invention at the time the instant patent application was filed. Applicant's arguments drawn to claims 2, 4-5, 7-8, 10-11, 25-26 and 32 have not been found persuasive and the rejection is maintained.

New Grounds of Objection

7. The specification is objected to because on page 5, line 12 the specification refers to SEQ ID NO2 as human SAG DNA. A review of the Paper Copy of the sequence listing reveals that SEQ ID NO:2 is a 113 amino acid sequence. Appropriate correction is required.

New Grounds of Rejection

Claim Rejections - 35 USC § 112

8. Claims 2-6, 8-17, 25-26, 32, 28-40 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make/use the invention.

The claims are drawn to an isolated and purified DNA molecule that hybridizes to SEQ ID NO:1/SEQ ID NO:3 and host cells transfected with said purified DNA molecules, SEQ ID Nos 11,13, 21, 23, 24, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 49, a diagnostic assay for detecting cells with mutations in a gene encoding a redox sensitive protein that protects from apoptosis using primers comprised by the DNA sequence of the pending claims, a method for purifying a protein, purified DNA encoding SEQ ID NOS 12, 4, 22,24, 26, 28, 30, 32, 34, 36,

38, 40, 42, 44, 46, 48 and 50, hybridizing DNA molecules that encode a polypeptide that protects against lipid peroxidation and apoptosis. The specification teaches that an OP-inducible gene, SAG, was isolated from two murine tumor cell lines (p. 13). Both a mouse and a human cDNA were identified and motif searching of the deduced protein sequence did not reveal any known functional domains, however, each deduced protein contained two imperfect heme binding sights and one imperfect zinc ring finger domain (p. 15). Further, SAG mRNA expression was found in all normal human tissues tested, with high expression levels in heart, skeleton muscle and testis, all of which consume high levels of oxygen (p. 17). NIH3T3 cells transfected with an SAG expression vector construct. Cysteine mutants of SAG in both the putative heme binding site and the zinc ring finger motif were produced and are recited in claims 15 and 38. These mutants were used to transform host cells and putative mutant SAG protein encoded by said host cells were produced and some mutants showed differential heme binding and differential oligomerization properties, compared to wildtype putative protein (p. 22 and Table 1) as measured *in vitro* (see Example 9, pgs 23-24). The putative SAG protein was shown to have no transactivational activity (p. 25). The putative SAG protein binds to polyU, polyA and polyC RNA but not to poly G or ssDNA (pages 25-26). Two deletion mutants of SAG mRNA were identified in a carcinoma cell line (SEQ ID Nos 11 and 13) (p. 26). The sensitivity of SAG-transfected cells to OP-induced apoptosis was assayed, the *in vitro* results suggest that overexpression of SAG protein protects cells against OP9 induced apoptosis as less DNA fragmentation was observed in wild-type SAG transfected cells compared to control cells. It is

noted that no data is presented, thus there is no way to determine from the specification whether the difference is significant or how much "less" is observed (p. 29). Additional *in vitro* experiments showed that antisense SAG expression inhibits tumor cell growth compared to vector control *in vitro* in SAG transfected colon cancer cells (p. 30). The specification suggests that since antisense SAG expression has been shown to inhibit tumor growth in cell lines transfected with a SAG expression construct (p. 31) that the SAG antisense construct would be useful for tumor treatment. The specification delineates prophetic exemplification of antisense gene therapy in an animal model (pages 31-32), prophetic exemplification of SAG function as a oxygen radical scavenger (p. 32), prophetic exemplification of prevention of IL-1beta induced brain injury by SAG administration (p. 33), prophetic example of human cancer diagnosis using SAG as a marker based on two SAG deletion mutants in human cancer cell lines originating from colon and testis (p. 33-34). In addition, SAG was shown to minimize or prevent LDL oxidation induced by copper ion or a free radical generator *in vitro* in a cell free assay (p. 37). SAG transfected into a human neuroblastoma cell line protected from metal induced apoptosis (para bridging pages 39-40) and which stimulated thymidine incorporation (p. 40).

One cannot extrapolate the teaching of the specification to the enablement of the claims because the only apparent asserted uses for the claimed nucleic acid molecule, other than the production of the protein encoded by the claimed nucleic acid molecule are (a) the inhibition of tumor cell growth by administration of an antisense to SAG, that is the treatment of cancer using antisense technology (b)

diagnosis of cancer by detecting deletion mutants of SAG polynucleotides, (c) use of the encoded protein as an oxygen radical scavenger. None of these uses is enabled for the reasons set forth below.

As drawn to the cancer treatment, the specification teaches a prophetic cancer gene therapy example in an animal model using adenovirus expressing antisense SAG. However, in the field of antisense technology, according to Gura (Science, 1995, 270:575-577), researchers have many concerns. Gura discloses that "the biggest concern is that antisense compounds simply don't work the way researchers once thought they did." Other drawbacks include difficulty getting antisense oligonucleotides to target tissues and the existence of potentially toxic side effects such as increased blood clotting and cardiovascular problems (page 575, col 1, para 2). Another problem stems from the fact that oligonucleotides used as controls produced the same biological effects in cell culture as did the antisense compounds (page 576, col 1, para 2 and 3). In addition, Gura reports problems with synthetic antisense oligonucleotides in that unwanted and sometimes lethal side effects occurred in animal experiments, and that they block cell migration and adhesion to underlying tissue *in vitro* (page 576, col 3, para 1 and 3). Thus a high degree of unpredictability is associated with the use of antisense constructs employed in methods of inhibiting expression of a particular protein. The specification clearly contemplates the use of said method *in vivo* in human subjects as well as in animal models for anti-sense therapy but does not address the issues raised by Gura.

Further, it was well known in the art at the time the invention was made that the status of the field of gene therapy in humans was unpredictable in regard to obtaining therapeutic levels of transcription in a host subject. Wang et al (PNAS, 1995, 92:3318-3322) specifically teach that therapeutic applications of antisense oligonucleotides are currently limited by their low physiological stability, slow cellular uptake and lack of tissue specificity (p. 3318, para 1). Problems with cellular uptake of antisense oligonucleotides are difficult to solve because endogenous uptake pathways generally have insufficient capacity to deliver the quantities of antisense oligonucleotides required to suppress gene expression and intracellular delivery and tissue specificity remain major obstacles to the implementation of antisense drugs in the treatment of human disorders (p. 3318, para bridging cols 1 and 2). Further, Orkin et al (Report and Recommendations of the Panel to Assess the NIH investment in Research on Gene Therapy, 1995) state that "while the expectations and the promise of gene therapy are great, clinical efficacy has not been definitively demonstrated at this time in any gene therapy protocol, despite anecdotal claims of successful therapy and the initiation of more than 100 Recombinant DNA Advisory Committee (RAC)-approved protocols" and further teach that significant problems remain in all basic aspects of gene therapy. In addition, Marshall (Science, 1995, 269:1050-1055) teaches that there has been no unambiguous evidence that genetic treatment has produced therapeutic benefits" (p. 1050, col 1) and that "difficulties in getting genes transferred efficiently to target cells - and getting them expressed - remain a nagging problem for the entire field" (p. 1054, col 3). James Wilson, one skilled in the art stated that "{t}he actual

vectors- how we're going to practice our trade - haven't been discovered yet" (p. 1055, col 2). Culver et al (TIG, 1994, 10:174-178) reviewing gene therapy for cancer, conclude that the "primary factor hampering the widespread application of gene therapy to human disease is the lack of an efficient method for delivering genes *in situ*, and developing strategies to deliver genes to a sufficient number of tumor cells to induce complete tumor regression or restore genetic health remains a challenge " (p. 178). Further, Orkin et al reports major difficulties at the basic level include shortcomings in all current gene transfer vectors and an inadequate understanding of the biological interaction of these vectors with the host. (see page 1). The specification contemplates the use of adenovirus expressing antisense SAG, however, none of the available vectors systems is entirely satisfactory and many of the perceived advantages of vector systems have not been experimentally validated, for example, a major disadvantage of the adenovirus vector system is its relatively high immunogenicity and the complexity of its genome. Hodgson (Exp. Opin. Ther. Patents, 1995, 5:459-468) discusses the drawbacks of viral transduction and states that "[d]eveloping the techniques used in animal models, for therapeutic use in somatic cells, has not been straightforward" (pp 5459-460). Miller et al (FASEB J., 1995, 9:190-199) also review the types of vectors available for *in vivo* gene therapy, and conclude that "for the long-term success as well as the widespread applicability of human gene therapy there will have to be advances..... targeting strategies outlined in this review, which are currently only at the experimental level, will have to be translated into components of safe and highly efficient delivery systems" (p. 198, col. 1). Finally, the research community, as reported by Nature Biotechnology,

1997, 15:815, has responded to the issues raised in the Orkin Report drawn to vector based delivery systems, that is the critical steps of delivery of a gene to the right cell and the subsequent maintenance of gene expression, since it is now widely appreciated that the natural tropism of a virus, while advantageous to its own replication cycle is not always optimal for a gene delivery protocol and a number of laboratories have explored methods to redirect the targeting that has evolved to ensure viral infectivity in ways that may be more suitable to the aims of gene therapy The author concludes that this return to first principles should help to continue to move gene therapy in the direction of its largest and most important ambitions (p. 815). Clearly, the issues raised by the Orkin report, although being addressed, have not been resolved. For the reasons set forth above, it cannot be predicted from the disclosure how to use the claimed DNA molecule for cancer treatment. For the above reasons, it appears that undue experimentation would be required to practice the claimed invention.

As drawn to diagnosis of cancer by detecting deletion mutants of SAG polynucleotides, one cannot extrapolate the teaching of the specification to the enablement of the claims because the asserted use appears to be based on the detection of two deletion mutants in a colon cancer cell line and in a testicular carcinoma cell line. However, no evidence has been presented that would suggest that SAG polynucleotides are mutated in any primary tumor. Further, it would appear, given that the claims are drawn to an encoded polypeptide that protects a cell from apoptosis and given that antisense transfection of SAG appears to reduce cancer cell proliferation, that overexpression of the SAG protein and not the

expected reduction of expression, through for example, the mutation and alteration of the polynucleotide encoding (and thence the encoded protein) would be the mechanism by which cancers are proliferated. Especially given the evidence that overexpression of SAG leads to increased thymidine incorporation, it is not clear how or why mutation of a SAG polynucleotide would useful to a cancer cell, since it would remove protection from apoptosis. Given the experimental evidence in the specification, that reduction of expression of the protein would not be expected to be associated either with the initiation or the progression of the disease. Further, it is well known in the art that characteristics of cultured cell lines generally differ significantly from the characteristics of a primary tumor. Freshney (Culture of Animal Cells, A Manual of Basic Technique, Alan R. Liss, Inc., 1983, New York, p4) teach that it is recognized in the art that there are many differences between cultured cells and their counterparts *in vivo*. These differences stem from the dissociation of cells from a three-dimensional geometry and their propagation on a two-dimensional substrate. Specific cell interactions characteristic of histology of the tissue are lost. The culture environment lacks the input of the nervous and endocrine systems involved in homeostatic regulation in vivo. Without this control, cellular metabolism may be more constant *in vitro* but may not be truly representative of the tissue from which the cells were derived. This has often led to tissue culture being regarded in a rather skeptical light (p. 4, see Major Differences *In Vitro*). Further, Dermer (Bio/Technology, 1994, 12:320) teaches that, "petri dish cancer" is a poor representation of malignancy, with characteristics profoundly different from the human disease Further, Dermer teaches that when a normal or

malignant body cell adapts to immortal life in culture, it takes an evolutionary -type step that enables the new line to thrive in its artificial environment. This step transforms a cell from one that is stable and differentiated to one that is not, yet normal or malignant cells *in vivo* are not like that. The reference states that evidence of the contradictions between life on the bottom of a lab dish and in the body has been in the scientific literature for more than 30 years. Further, it is not clear whether the deletion mutations in the colon and testicular cell lines are artifacts of the cell culture system of these particular neoplastic cell lines or whether this can be in any way related to the *in vivo* cells from which the cell line was derived, in view of the art recognized problems with artifacts associated with cell culture. For example, Drexler et al (Leukemia and Lymphoma, 1993, 9:1-25) specifically teach, in the study of Hodgkin and Reed-Sternberg cancer cells in culture, that the acquisition or loss of certain properties during adaptation to culture systems cannot be excluded. This is exemplified by the teachings of Zellner et al (Clin. Can. Res., 1998, 4:1797-1702) who specifically teach that products are overexpressed in glioblastoma (GBM)-derived cell lines which are not overexpressed *in vivo*. Drexler et al further teach that only a few cell lines containing cells that resemble the *in-vivo* cancer cells have been established and even for the bona fide cancer cell lines it is difficult to prove that the immortalized cells originated from a specific cancer cell (see attached abstract). Further, Embleton et al (Immunol Ser, 1984, 23:181-207) specifically teaches that in procedures for the diagnosis of osteogenic sarcoma, caution must be used when interpreting results obtained with monoclonal antibodies that had been raised to cultured cell lines and specifically teach that cultured tumor

cells may not be antigenically typical of the tumor cell population from which they were derived and it is well established that new artifactual antigens can occur as a result of culture (see attached abstract). Hsu (in Tissue Culture Methods and Applications, Kruse and Patterson, Eds, 1973, Academic Press, NY, see abstract, p.764) specifically teaches that it is well known that cell cultures *in vitro* frequently change their chromosomal constitutions (see abstract). Thus, based on the cell culture data presented in the specification, in the absence of data provided from primary tumor cells and normal controls, no one of skill in the art would believe it more likely than not that the claimed invention could be used as contemplated or as claimed in claims 25 and 26. For the above reasons, it appears that undue experimentation would be required to practice the claimed invention.

As drawn to the encoded protein, the apparent asserted uses for the protein encoded by the claimed nucleic acid molecule are for protection against lipid oxidation, for protection against apoptosis. As drawn to protection against lipid oxidation the specification presents a cell free assay to support the asserted use. However, the exemplified assay is not commensurate in scope with the asserted use of the claimed invention. The specification does not teach now to make the process, does not teach in what environment to use the protein or how to implement the method. The specification provides insufficient guidance with regard to these issues and provides no working examples which would provide guidance to one skilled in the art as to how to use the asserted and claimed invention with a reasonable expectation of success. For the above reasons, it appears that undue experimentation would be required to practice the claimed invention.

As drawn to protection against apoptosis, the specification provides no guidance or exemplification on how to use this process. Clearly, one of skill in the art would not use the encoded protein to protect cancer cells from apoptosis (as exemplified in the specification). No system wherein the encoded protein would be useful to protect that system from apoptosis has been identified and no evidence or guidance has been presented that would suggest that the encoded protein could accomplish the process, even if the place to accomplish this process were identified, *in vivo*. The specification provides insufficient guidance with regard to these issues and provides no working examples which would provide guidance to one skilled in the art as to how to use the asserted and claimed invention with a reasonable expectation of success. For the above reasons, it appears that undue experimentation would be required to practice the claimed invention.

As drawn to the use as an oxygen radical scavenger, Example 19 states that the SAG protein demonstrates some oxidative buffering activity and that this activity **may** qualify SAG as an oxygen radical scavenger (emphasis added) and suggests an assay, in yeast, to determine whether SAG is an effective oxygen radical scavenger. Example 20 presents a protocol to determine whether SAG, in its putative scavenger capacity, can prevent IL-1beta induced brain injury during ischemia. It is clear from the teaching in the specification that Applicant cannot predict whether or not the encoded protein will function as claimed. The specification provides insufficient guidance with regard to these issues and provides no working examples which would provide guidance to one skilled in the art as to how to use the asserted and claimed invention with a reasonable expectation of success. For the above reasons,

it appears that undue experimentation would be required to practice the claimed invention.

9. If Applicant were able to overcome the rejection under 35 USC 112, first paragraph above, claims 15-17, 25-26, 32 and 38 would still be rejected under 35 USC 112, first paragraph because the specification, while being enabling for SEQ ID Nos 1 and 3 as well as vectors and host cells comprising said sequences, methods of making the encoded polypeptide wherein said polypeptide protects a cell from apoptosis when produced in said cell, protects against lipid peroxidation, does not reasonably provide enablement for mutants of SEQ ID NOS 1 and 3. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The claims are drawn to DNA mutants of SEQ ID Nos 1 and 3 and to isolated DNA sequences encoding polypeptides having the amino acid sequences encoded by the specifically claimed mutants of SEQ ID Nos 1 and 3. The specification teaches that two deletion mutants of SAG polynucleotide were detected in carcinoma cell lines (SEQ ID Nos 11 and 13)(p. 26) and that transfection of those mutant constructs into host cells did not produce proteins that were detectable by the antibody used to detect SAG protein expression of wild-type transfectants (p. 28). The specification further teaches the production of 15 mutants, recited in Table 1 (p. 22) wherein mutants were mutated in either the heme site or the zinc ring finger site (p. 23). One cannot extrapolate the teaching of the specification to the scope of the claims because, as drawn to mutants SEQ ID NOS

11 and 13, it is not clear that a protein is even produced. Further, even if a protein were to be produced, it is well known in the art that protein chemistry is probably one of the most unpredictable areas of biotechnology. For example, replacement of a single lysine reside at position 118 of acidic fibroblast growth factor by glutamic acid led to the substantial loss of heparin binding, receptor binding and biological activity of the protein. Burgess et al. J of Cell Bio. 111:2129-2138, 1990. In transforming growth factor alpha, replacement of aspartic acid at position 47 with alanine or asparagine did not affect biological activity while replacement with serine or glutamic acid sharply reduced the biological activity of the mitogen. Lazar et al. Molecular and Cellular Biology 8:1247-1252 (1988). Similarly it has been shown that a glycosylation of antibodies reduces the resistance of the antibodies to proteolytic degradation, while CH2 deletions increase the binding affinity of the antibodies. These references demonstrate that even a single amino acid substitution or what appears to be an inconsequential chemical modification will often dramatically affect the biological activity and characteristic of a protein. The effect of the differences in the mutants, compared to the wild-type, cannot be predicted. It is impossible to determine, given the information in the specification, for example, whether or not, or which of the claimed encoded mutant species protects cells from apoptosis, protects against lipid peroxidation, acts as an oxygen/radical scavenger.

Further, as drawn to antisense therapy, it is not clear how the mutations recited will affect antisense molecules and no teaching has been made of how to determine, in the mutants, which antisense molecules would function to treat cancer. Finally, as drawn to diagnosis of cancer, there is no teaching in the specification or

in the art of record that any of the recited mutants are associated in any way with any type of cancer. For the above reasons, it appears that undue experimentation would be required to practice the claimed invention.

10. Claims 25-26 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 25-26 are indefinite in the recitation of "A diagnostic assay". The claim is indefinite because it is not clear what the assay is diagnostic for. The metes and bounds of the claimed patent protection cannot be determined.

Claim Rejections - 35 USC § 102

11. The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371© of this title before the invention thereof by the applicant for patent.

12. Claims 2 and 9 are rejected under 35 USC 102(b) as being anticipated by Boehringer Mannheim Biochemicals, 1994 Catalog, p. 93).

The claims are drawn to a DNA molecule that hybridizes to SEQ ID NO:1/3 under the claimed hybridization conditions.

The Boehringer Mannheim teaches a kit comprising random primers that encompass all possible 6-nucleotide sequences (see page 93, Catalog No. 1034 731/1006 924), a subset of which will hybridize to the claimed sequences under the claimed conditions. All of the limitations of the claims are met.

13. All other objections and rejections recited in Paper No. 13 are withdrawn.

14. No claims allowed.

15. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Susan Ungar, PhD whose telephone number is (703) 305-2181. The examiner can normally be reached on Monday through Friday from 7:30am to 4pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, can be reached at (703) 308-3995. The fax phone number for this Art Unit is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Effective, February 7, 1998, the Group and/or Art Unit location of your application in the PTO has changed. To aid in correlating any papers for this

application, all further correspondence regarding this application should be directed to Group Art Unit 1642.

Susan Ungar
Primary Patent Examiner
July 24, 2002